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# The Relationship Between Vitamin D Deficiency and Cognitive Decline in the Geriatric Population

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# The Relationship Between Vitamin D Deficiency and Cognitive Decline in the Geriatric Population

## **Abstract**

**Background:** The role that vitamin D plays in numerous biological systems has been an intriguing topic in recent decades. Currently, scientists are researching its interaction with the central nervous system, and in particular, the ageing brain. Substantial data from animal research exist on the physiologic effects of vitamin D on the neurological system. It is postulated that this vitamin may influence cognitive function in humans.

**Methods:** Using the search terms “vitamin D” and “cognitive function,” an exhaustive literature search was performed using the following databases: Medline-OVID, Web of Science, MD Consult, CINHALL, and PsycINFO. Any other scientific terms that can be used for these two terms were searched, as well, including but not limited to “cholecalciferol” and “cognition” and “cognitive decline” so that relevant research articles were not overlooked. Articles pertaining to the clinical question were then appraised and assigned a validity score.

**Results:** Five articles met the inclusion and exclusion criteria for the systematic review. All of the articles were observational studies. The results of three of them found a positive correlation between vitamin D levels and cognitive function, while the results of other studies did not reveal an association between the two variables.

**Conclusion:** The articles included in this study did not reach a collective agreement on an answer to the clinical question posed. Future research is warranted on this topic due to its potential impact on managing elderly medical care, and it should focus on the efficacy of using supplemental vitamin D to decrease risk of age-related cognitive decline.

## **Degree Type**

Capstone Project

## **Degree Name**

Master of Science in Physician Assistant Studies

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## **Keywords**

vitamin D, cognition

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**Subject Categories**

Medicine and Health Sciences

**Rights**

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# **The Relationship Between Vitamin D Deficiency and Cognitive Decline in the Geriatric Population**

Erin Walker



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 14, 2010

Faculty Advisor: Mary Von, MS, PAC

Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD

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# Biography

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[Redacted for privacy]

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# Abstract

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**Background:** The role that vitamin D plays in numerous biological systems has been an intriguing topic in recent decades. Currently, scientists are researching its interaction with the central nervous system, and in particular, the ageing brain. Substantial data from animal research exist on the physiologic effects of vitamin D on the neurological system. It is postulated that this vitamin may influence cognitive function in humans.

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**Keywords:** vitamin D, cognition



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To my parents and brother, thank you for your infinite encouragement and support while I pursued my dreams.

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## List of Abbreviations

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AD	Alzheimer's Dementia
ADL	Activities of daily living
CDR	Clinical Dementia Rating
CI	Confidence Interval
CT	Computerized Tomography
MMSE	Mini Mental Status Exam
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
RCT	Randomized Controlled Trial
SBT	Short Blessed Test
VDR	Vitamin D Receptor

# **The Relationship Between Vitamin D Deficiency and Cognitive Decline in the Geriatric Population**

## **BACKGROUND**

### **Overview**

Vitamin D has been under much scrutiny in recent decades for its effects on many biological systems. The earliest research studies addressed its actions in calcium homeostasis and bone formation.<sup>1,2</sup> Currently, it is postulated that this vitamin may interact with the immune, cardiovascular, musculoskeletal, endocrine, and nervous systems.<sup>1,3-6</sup> New studies are exploring its interaction with the central nervous system and, in particular, the ageing brain.<sup>6</sup> Numerous studies have found vitamin D receptors (VDRs) in locations of the brain involved in cognition, such as the cortex, hypothalamus, and substantia nigra.<sup>5-8</sup> Also, metabolic pathways have been discovered in the cerebellum and hippocampus, suggesting vitamin D's role in basic cognitive function, executive function, and formation of memories.<sup>4,5</sup> Robust data from in vitro and animal studies suggest that vitamin D has neuroprotective properties, indicating that it may contribute to the prevention of neurodegenerative disease in ageing individuals.<sup>1,2,4,6,7,9-11</sup>

### **Mechanism of Vitamin D**

Vitamin D is a multipurpose, fat-soluble, seco-steroid hormone.<sup>5,6,8</sup> The two most important forms of vitamin D are cholecalciferol (vitamin D<sub>3</sub>) and ergocalciferol (vitamin D<sub>2</sub>).<sup>1</sup> The former is produced in the skin by sunlight, while the latter is contained in some fruits and vegetables and fortified foods.<sup>1</sup> These forms of vitamin D are inactive until they are metabolized by the liver and kidney.<sup>1</sup> Once biologically active, vitamin D binds to intracellular VDRs, such as those expressed on neurons.<sup>1,8</sup> It is the interaction with these VDRs that enables vitamin D to act on a cellular level.<sup>12</sup> Serum 25(OH)D is the active metabolite of cholecalciferol and ergocalciferol that is usually measured to determine the Vitamin D status of an individual.<sup>8</sup>

### Prevalence of Vitamin D Deficiency

Hypovitaminosis D is prevalent among older adults<sup>5,13</sup> due to both low dietary intake and inadequate sun exposure.<sup>6,13</sup> As many as fifty to eighty percent of elderly people have low vitamin D levels.<sup>14</sup> However, due to lack of screening, the proportion of the geriatric population that has unrecognized vitamin D deficiency may be much larger.<sup>15</sup> Those at highest risk for low vitamin D status include individuals with low sunlight exposure, females, those with poor nutrition, people who have dark pigmented skin, and the elderly.<sup>3</sup> There is some discrepancy about how much of the vitamin is enough. Vitamin D deficiency is defined by some as a 25(OH)D value less than 20ng/mL.<sup>16</sup> Some researchers further separate the categories into insufficiency (values less than 10ng/mL), deficiency (values from 10-20ng/mL), and sufficiency (values greater than 20ng/mL).<sup>4</sup> Yet, others use a less lenient value to define deficiency (any value less than 25ng/mL).<sup>17</sup>

### Dementia and Cognitive Decline

Dementia is defined as cognitive decline resulting in memory deterioration and impaired daily functioning<sup>4</sup>, and its development may involve several mechanisms.<sup>10</sup> Signs and symptoms of decreased cognition in persons of advanced age are connected to both biological and environmental factors.<sup>18</sup> By determining the role that vitamin D plays in these mechanisms, researchers have the capacity to improve overall health and decrease morbidity in the aging population.

The geriatric population is rapidly growing, and individuals eighty-five years old or older compose the group that is increasing the fastest.<sup>4</sup> Memory problems are reported by the majority of elderly patients.<sup>18</sup> It is known that memory is related to other cognitive abilities such as attention, executive control, learning, and problem-solving.<sup>18</sup> Deficits in these areas can be disabling and debilitating in these individuals. Studies have shown that there are higher mortality rates and increased risk of future nursing home admission in older adults with low vitamin D levels.<sup>5,13</sup> As the number of elderly patients increases, undoubtedly, the number of individuals with dementia and cognitive

dysfunction will rise. The impact that this may have on society would be immense, having the potential to drain health care resources and increase medical costs system-wide.

### **Purpose of Study**

The majority of evidence regarding the action of vitamin D in the central nervous system and its effects on cognitive function comes as a result of experiments performed on laboratory rats or mice.

<sup>2</sup> Evidence that vitamin D is involved in brain function is strong; however, studies measuring its impact on human cognition yield mixed results. <sup>2</sup> The purpose of this study is to conduct a systematic review of recent research articles regarding vitamin D and cognitive decline in the elderly population to determine if any correlation can be found between the two variables.

### **Clinical Question and its Significance**

Answering the question of whether or not vitamin D has an impact on cognitive function in the elderly is clinically relevant because it may impact how and when clinicians screen for vitamin D deficiencies and may propel future research in the direction of examining the efficacy of vitamin D supplementation for management or prevention of dementia in the geriatric population.

## **METHODS**

### **Description of Search**

An exhaustive literature search was performed using the following databases: Medline-OVID, Web of Science, MD Consult, CINAHL, and PsycINFO. The search was executed using the following terms: vitamin D, dementia, cognition, cognitive decline, and cognitive dysfunction. References from the bibliographies of articles found in the initial search were obtained and were also utilized.

### **Eligibility Criteria**

This systematic review included studies in which cognitive status or dementia was measured, serum 25(OH)D was a measured outcome, and an association between the two measurements was explored. Articles published after 2000 were included in the systematic review. All articles used were full-text and published in the English language.

## **Assessment of Validity**

Articles that met the eligibility criteria were then critically appraised in order to evaluate their validity. A scoring system was created so that validity criteria could be used to assess the reliability of each of the articles. Figure I shows the validity scoring system used. Each article was assigned a numerical value based upon the number of criteria it met.

## **Exclusion Criteria**

Articles scoring 3/7 or less on the self-created validity scoring system were excluded from the formal review of literature. Articles were excluded if the study sample included participants less than sixty years of age. Other systematic reviews on this topic were excluded from the formal analysis of this systematic review of literature.

## **RESULTS**

Five studies met the inclusion/exclusion criteria mentioned in the methods section. All five studies were observational studies, and were able to be compared to each other when necessary. Three of these studies showed a positive association between cognitive function and vitamin D status. On the other hand, two of the research articles found there was no association between the two variables.

### **Summary of Studies**

*25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services*<sup>21</sup> (2010) was a retrospective chart review of four years of data collected between 2003 and 2007. The study used urban-dwelling subjects who partook in homecare services. Participants in this study were low income, had diminished ability to perform activities of daily living (ADLs), and had unmet needs such as food or personal care. There were 305 subjects who were evaluated for vitamin D deficiency and cognitive decline. Subjects were assigned diagnoses of dementia or no cognitive decline using criteria from the National Institute of Neurological and Communicative Disorders, Stroke-Alzheimer's Disease and Related Disorders Association, and DSM-IV. Magnetic Resonance Imaging (MRI) of the brain was performed on each of the subjects. Logistic regression models were used to

evaluate the associations between vitamin D levels and diagnoses of Alzheimer's disease (AD), all-cause dementia, and stroke. Adjustments in analysis were made for covariates such as age, BMI, plasma homocysteine, physical activity, gender, ethnicity, education level, ApoE allele status, diabetes, hypertension, and multivitamin use. The results revealed that 25(OH)D insufficiency (<20ng/mL) was associated with more than two times the risk of all-cause dementia and AD after all adjustments were made.

*Higher serum vitamin D<sub>3</sub> levels are associated with better cognitive test performance in patients with Alzheimer's disease*<sup>8</sup> (2008) was a cross-sectional observation study. It chose its sample population from a group of 962 patients referred to a geriatric outpatient clinic. Of these patients, 225 were diagnosed with probable AD and underwent laboratory testing for vitamin D levels. Patients were excluded for taking any vitamin supplementation at the time of investigation. Dementia and AD was diagnosed according to DSM-IV and NINCDS-ADRDA criteria, respectively. Patients were placed into vitamin D categories. Vitamin D-sufficient subjects had >20ng/mL serum 25(OH)D levels, while vitamin D-insufficient and deficient subjects had 10-19.9ng/mL and <10ng/mL, respectively. Linear regression models were utilized to determine relationships between MMSE score and vitamin D levels. Analysis showed positive association between serum 25(OH)D levels and MMSE score ( $p < 0.001$ ). After adjusting for cofactors such as sunlight exposure and educational background, the association remained statistically significant ( $p=0.01$ ).

*Vitamin D is associated with cognitive function in elders receiving home health services*<sup>4</sup> (2009) was a cross-sectional retrospective chart review that selected subjects from the same population that was used for the *25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services*<sup>21</sup> article mentioned above. The study sample for this paper, however, was much larger. Its sample size was 1,080. Another difference between this study and the other was that subjects underwent a neuropsychological battery of tests by trained research assistants which included testing verbal intelligence, auditory and visual retention, executive function, mental processing speed,



visual construction, fluid reasoning, and verbal fluency. Univariate and multiple regression models were constructed to look at associations of serum 25(OH)D concentration and cognitive function. The authors found significant associations between vitamin D concentration and the executive function, attention, and processing speed factors, even after covariate adjustment ( $p < 0.01$ ). Low vitamin D levels were associated with impairments in cognitive function, mostly in areas of executive functioning (planning for the future, problem solving, or sequencing) and processing speed. However, no relationship was noted between memory and vitamin D levels.

*Blood biomarkers of osteoporosis in mild cognitive impairment and Alzheimer's disease*<sup>17</sup> (2009) was a case-controlled observational study which found no correlation between vitamin D and AD. Subjects for this article were recruited from an outpatient clinic and assigned to groups based upon diagnosis of mild cognitive impairment, mild AD, and cognitively normal controls. Diagnoses were made by a psychiatrist, psychologist, and radiologist based upon the results of the following examinations: comprehensive psychometric testing, CT or MRI brain imaging, extensive blood screening, physical examination, and detailed medical history. The sample size was 47 (19 in the mild cognitive impairment group, 20 in the AD group, and 8 in the cognitively normal group). A large battery of tests was used to assess cognitive levels in the subjects. This battery included but was not limited to MMSE, Clockdrawing Test, Trail Making Test, Global Deterioration Scale, and Clinical Dementia Rating Scale. Two-sided  $t$  tests were used for all primary group comparisons of biochemical data. Two-sided Pearson correlation analyses were calculated for age and biochemical markers and MMSE scores. No statistically significant difference was discovered between the vitamin D levels of the controls versus those of the AD and mild cognitive impairment groups.

*25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men*<sup>16</sup> (2009) was unique in that it was a prospective cohort study which explored the temporal relationship between the two variables to see if fluctuations in vitamin D in an individual correlated with variations in the individual's cognitive function. The sample population was composed of 1,138 community-dwelling

male subjects who were recruited from several different urban cities in the United States. The subjects were included in a prospective analysis of follow-up on cognitive decline. Cognitive function was assessed by a trained technician with the 3MS and Trails B tests at baseline and at the follow-up examination. Logistical regression models were used to examine the relationship between baseline 25(OH)D level and odds of cognitive impairment and decline. Serum 25(OH)D was expressed in various ways. It was expressed in quartiles, as a dichotomous variable, and as a continuous variable. Analyses were adjusted for age, clinic site, season of blood draw, ethnicity, education, age, self-reported health status, ADL impairments, smoking, alcohol consumption, BMI, and physical activity level. Before adjusting for the cofactors, men with lower vitamin D levels had increased odds of cognitive impairment at baseline. After adjusting for education level and ethnicity, there were no statistically significant associations between vitamin D and cognitive levels. In models adjusted for age, season, and study site, there was an association between lower vitamin D levels and odds of cognitive decline as defined by only one of the cognitive measures, the 3MS ( $p=0.04$ ). After further adjusting the models for ethnicity and education level, the association was decreased to the point that it was not statistically significant.

## **DISCUSSION**

The purpose of this paper was to explore the association between vitamin D and cognition in the elderly. Five articles from 2000-2010 met the inclusion/exclusion criteria of this systematic review. The articles included in this study did not reach a collective agreement on an answer to the clinical question posed.

Even though all five studies were observational, they had differing designs. For example, two of the studies were case-controlled. These studies had the ability to compare vitamin D levels between those with and without cognitive dysfunction, allowing prediction of an odds ratio or relative risk. Four of the five studies made adjustments in their statistical analyses for covariates. Adjusting for confounding factors limits outcome bias by accounting for participant characteristics that may affect

one of the outcomes being measured. Only one study was longitudinal, exploring the temporal relationship between vitamin D levels and cognitive function.

### **Limitations of Study**

Each study had its own inherent limitations. In *25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services*<sup>21</sup> (2010), the limitations of the study were that it was a cross-sectional study, so no temporal relationships between the two variables were explored. Also, participants were recruited from social services, so they cannot be generalized to a community-dwelling population. Lastly, no control group was used for comparison. The study entitled *Higher serum vitamin D<sub>3</sub> levels are associated with better cognitive test performance in patients with Alzheimer's disease*<sup>8</sup> (2008) was unable to assess if cognitive levels fluctuated with changes in vitamin D status over time, and it did not compare the study group to a control group. Of most concern is that this study used only one measure of cognitive function (the MMSE) to assess the relationship between cognition and vitamin D status. *Vitamin D is associated with cognitive function in elders receiving home health services*<sup>4</sup> (2009) had similar limitations to the ones described above. The sample is not representative of the general population. No temporal relationships can be deciphered from the data, and again, no case controls were utilized. The main limitation of *Blood biomarkers of osteoporosis in mild cognitive impairment and Alzheimer's disease*<sup>17</sup> (2009) was the very small sample size, which decreased the chance that findings would be statistically significant. Another limitation was that linear regression models were not used to evaluate the relationship between levels of vitamin D and levels of cognition. This study, unlike the others, did not make adjustments in its analysis to account for covariates that may have affected the outcomes. Yet another problem was that similar to the other studies in this review, this was not a longitudinal study, so no inferences can be made upon the temporal relationship between vitamin D and cognition. The problems of the study, *25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men*<sup>16</sup> (2009) were three-fold. The sample was all male and mostly white and is not generalizable to the elderly population.

Participants who did not follow-up for the prospective portion of the study tended to be older, frailer, and had lower baseline vitamin D levels and lower baseline cognitive function than those who did follow-up. This may have skewed the prospective results. Lastly, a relatively small battery of tests was utilized to assess cognition.

One feature that all the studies shared was that they were observational studies. Although this makes it easier to compare and contrast the studies with one another, the lower validity of observational studies must be taken into consideration. Because observational studies are per se less valid than randomized controlled trials (RCTs), bias, confounding, and chance must be thoroughly assessed in each study.<sup>19</sup>

Other reasons for the discrepancies between the studies' results can be estimated by examining the variations in sample populations, outcome measurements, and methodology between the five studies. The observational design of these studies did not allow any randomization in the sample populations, which made it difficult to compare and contrast between the studies and, thus, limited the ability to apply the results to the general geriatric population. Also the sample sizes of the studies were not impressively large. In fact, one of the studies in this review had fewer than 100 participants, although the study fit this systematic review's inclusion/ exclusion criteria. Statistically significant results are a challenge to obtain with such a small sample.

Although serum 25(OH)D measurement methods were uniform among the studies, the measurement of cognitive function, cognitive decline, and dementia were vastly inconsistent. Each study used different quantities and types of assessments to measure cognition as an outcome. This poses a constraint on making comparisons between studies.

### **Recommendations for Future Studies**

In order to answer the clinical question as to whether or not an association exists between cognitive function and vitamin D levels in geriatric patients, more research is warranted. This research should utilize randomized controlled trials to increase the validity of the results. Another suggestion is

that future study analyses should adjust for confounding variables to limit characteristics that may independently contribute to the outcome of interest. Future studies would also benefit from using some standardized outcome measurement of cognition. Maybe researchers could determine the most effective and accurate manner of quantifying cognitive levels in the elderly. Some sort of consistent protocol could help to consolidate results among various research studies and aid in the interpretation of the results.

Another way that this clinical question can be addressed is to assess whether or not vitamin D supplementation protects against cognitive decline in the elderly. This could be undertaken by designing placebo-controlled interventional studies. Additionally, long prospective cohort studies could be utilized to determine if correction of vitamin D deficiency in the elderly could prevent cognitive decline in this population.

## **CONCLUSION**

Although there is substantial data on the physiologic effects of vitamin D on the central nervous system as demonstrated by research on animals, there is not sufficient data on humans to conclude a correlation between this vitamin and cognitive function. Furthermore, too few studies of high validity have been performed on the geriatric population to discern a relationship between age-related cognitive decline and vitamin D levels. Future research is warranted on this topic due to its potential impact on managing elderly medical care. In particular, future research should focus on the efficacy of using supplemental vitamin D to decrease the risk of age-related cognitive decline, thus reducing overall morbidity in this continually growing age group.

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## TABLES

Table I. Summary of Critically Appraised Articles

Author/ Year	Study type	Population	Comparison	Outcome(s)	Validity Score
Przybleski et al <sup>20</sup> (2006).	Retrospective chart review	32 patients age >60 that had been referred for assessment of memory loss behavior problems associated with cognitive impairment.	None	Serum Vit D. concentration and Mini Mental Status Exam (MMSE) showed a significant positive correlation (p=0.006).	1
Wilkins et al <sup>15</sup> (2006).	Cross- sectional observational study	40 patients with mild AD age > 60.	40 patients with no dementia.	Vitamin D deficiency was associated with impairment on 2 of 4 measures of cognitive performance.	3
McGrath et al <sup>11</sup> (2007).	Retrospective observation of a survey	3 groups: 1,676 adolescents (age 12- 16), 4,747 adults (age 20-59), 4,808 elderly (age 60-90).	None.	In elderly group, those with the highest Vitamin D levels demonstrated the most impairment on the memory task. In the adolescent and adult group, there was no association between performance and vitamin D levels.	3
Oudshoorn et al <sup>8</sup> (2008).	Cross- sectional observational study	225 outpatients with diagnoses of probable AD age >60.	None.	Vitamin D-sufficient patients had significantly higher MMSE scores as compared to vitamin-D- insufficient ones.	4
Luckhaus et al <sup>17</sup> (2009).	Cross- sectional observational study	3 groups: 19 patients with mild cognitive impairment, 7 with primary osteoporosis, 20 with AD.	8 cognitively normal age- matched controls	Vitamin D levels were of equal amounts in the control group, mild cognitive impairment group, and Alzheimer's dementia group.	5
Buell et al <sup>21</sup> (2010).	Cross- sectional observational study	4 groups totaling 318. 41 with AD, 22 stroke with dementia, 76 all- cause dementia.	211 no stroke or dementia.	Mean vitamin D concentrations were lower in subjects with dementia	4
Buell et al <sup>4</sup> (2009).	Cross- sectional observational study	1,080 elders > age 65.	None.	Vitamin D was associated with executive function and attention and processing speed factors, but not the memory factor.	4
Slinin et al <sup>16</sup> (2009).	Prospective cohort study	1,376 community- dwelling men age >65.	None	After adjusting for covariates, there was no association between vitamin D level and cognitive impairment by 3MS testing or the Trails B test.	4

Table II. Summary of Reviewed Articles

	Study Name	Outcome(s)	Validity Score
<b>Positive Correlation</b>	Oudshoorn et al. <i>Higher serum vitamin D3 levels are associated with better cognitive test performance in patients with Alzheimer's disease</i> <sup>8</sup> (2008).	Vitamin D-sufficient patients had significantly higher MMSE scores as compared to vitamin-D-insufficient ones.	4
	Buell et al. <i>25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services</i> <sup>21</sup> (2010).	Mean vitamin D concentrations were lower in subjects with dementia	4
	Buell et al. <i>Vitamin D is associated with cognitive function in elders receiving home health services</i> <sup>4</sup> (2009).	Vitamin D was associated with executive function and attention and processing speed factors, but not the memory factor.	4
<b>No Correlation</b>	Luckhaus et al. <i>Blood biomarkers of osteoporosis in mild cognitive impairment and Alzheimer's disease</i> <sup>17</sup> (2009).	Vitamin D levels were of equal amounts in the control group, mild cognitive impairment group, and Alzheimer's dementia group.	5
	Slinin et al. <i>25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men</i> <sup>16</sup> (2010).	After adjusting for covariates, there was no association between vitamin D level and cognitive impairment by 3MS testing or the Trails B test.	4

Table III. Validity Scoring System

Validity Criteria	Numerical Value
Sample size > 100.	1
Control or comparison group was utilized.	1
Control group was age-matched.	1
>1 cognitive test was used to diagnose dementia.	1
Stage or severity of dementia was described.	1
Adjustments for cofactors were made in statistical analysis.	1
Study was longitudinal.	1
<b>Total Score (out of 7) _____</b>	

Table IV. Summary of Cognitive Assessments

Test Name	Description
Mini Mental Status Exam (MMSE)	Tool commonly used to measure five areas of cognitive function. It assesses orientation, registration, attention and calculation, recall, and language. The maximum score is 30, with a score of 23 or less indicating cognitive impairment. It takes 5-10 minutes to administer. <sup>22</sup>
Short Blessed Test (SBT)	Initial screening test that is sensitive to early changes associated with Alzheimer's disease. Higher scores are suggestive of impairment consistent with dementia, and an additional cognitive assessment is recommended. Scores in the normal range suggest that a dementing disorder is unlikely. <sup>23</sup>
Clinical Dementia Rating (CDR)	Rates cognitive performance in each of six categories: memory, orientation, judgment and problem-solving, community affairs, home management and hobbies, and personal care. CDR of zero indicates no dementia, while a CDR of 3 indicates severe dementia. <sup>15</sup>
CDR Sum of Boxes Score	Summation of the individual scores in the six CDR categories. Ranges from zero to eighteen. <sup>24</sup>
3MS	Test of global cognitive function, with scores ranging from zero to 100. Higher scores represent greater cognitive function. <sup>16</sup>
Trails B	Test of executive function, assessing "attention, concentration, psychomotor speed, cognitive shifting, and complex sequencing function by measuring the time required to connect a series of sequentially numbered and lettered circles". Test score is affected by age, education, and general intelligence. Outcomes measured in times; shorter times indicating better executive function. <sup>16</sup>